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Synthesis, cytotoxic activities and photophysical properties of 7-amino-4-methylcoumarin based 1,4-di substituted 1,2,3-triazole derivatives by "Click" chemistry

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ABSTRACT

The present study will focus mainly on the new series of 1,2,3- triazoles linked with 7-amino-4-methyl coumarin (**4**) are synthesized using Click reaction. All the newly synthesized compounds (**7a-q**) are characterized by analytical and spectroscopic methods (IR, HRMS, ^{1}H and ^{13}C-NMR) and subjected to cytotoxicity screening against a panel of six different human cancer cell lines viz. Hela, PANC1, HepG2, SKNSH, MDAMB and IMR 32 cell lines. Interestingly, among the tested molecules, some of the analogs displayed better cytotoxic activity. Out of the synthesized triazoles (**7a-q**), compounds **7h, 7i** and **7l** showed potent activity, as **7h** and **7l** showed more potent activity against IMR32 cell line with GI_{50} of 0.015 and 0.02 μM, respectively and **7i** with GI_{50} of 0.02 μM against SKNSH cell line. Further photophysical properties (UV & fluorescence) for these compounds (**7a-q**) are also discussed.

Keywords: 1,3-Dipolar cycloaddition, 1,2,3-Triazole, Cytotoxic & photophysical properties.

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INTRODUCTION

Coumarins are plant-derived natural products known for their enormous spectrum pharmacological properties such as antioxidant[1], anti-inflammatory[2], antimicrobial, anticoagulant, antiviral, anticancer, antihypertensive, anticonvulsant, antiadipogenic, antihyperglycemic [3]. In addition to this, aminocoumarin antibiotics clorobiocin (also spelled chlorobiocin), novobiocin, and coumermycin are potent inhibitors of DNA gyrase produced by different *Streptomyces* strains and anti HIV [4-6] Coumarins are also used as flavoring agent in a variety of foods (soft drinks, yogurt, and muffins) and biofilms [7]. Coumarins like imperatorin and esculetin showed anti-cancer [8] and antitumor activity [9] respectively. Osthole is very effective in inhibiting the migration and invasion of breast cancer by wound healing and transwell assays [10] and has been found to rescues cultured primary neurons from *N*-methyl-D-aspartate toxicity[11] and chartreusin exhibited antitumor properties against murine L1210, P388 leukemias, and B16 melanoma [12].

Knowing the importance of coumarin, and pharmacological activities of the triazole derivatives such as anti-cancer[13-16], anti-inflammatory[17], antibacterial, anticonvulsant[18], antiviral [9], antifungal [20], immunosuppressant[21], etc., and molecular hybridization strategy to develop hybrid multifunctional molecules[22] and in continuation of our efforts on the synthesis of heterocyclic compounds[23, 24] , we have synthesized a series of novel 1,4-disubstituted 1,2,3-triazole on keeping the 7-amino-4-methyl coumarin moiety as the starting point and are presented herein for the first time.

MATERIALS AND METHODS

All the chemicals and reagents used were of analytical grade from Sd fine, Sigma, and Merck unless otherwise specified. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (KBr pellets) in cm^{-1} were recorded on a “BOMMEN” IR spectrophotometer. Silica gel (100- 200 mesh) was used for the column chromatography. TLC plates (Silica Gel 60 F254) were used for thin-layer chromatography (TLC) and spots were visualized under UV irradiation. NMR spectra were recorded on ^1H and ^{13}C NMR spectra for analytical purpose were recorded in $CDCl_3$, DMSO-d_6 on a Bruker instrument at 300 MHz and 75 MHz, respectively; chemical shifts are expressed in δ-scale downfield from TMS as an internal standard. All ^1H and ^{13}C NMR chemical shifts are quoted in ppm and were calibrated on solvent signals. Multiplicities are given as s (singlet), d (doublet), dd (doublet– doublet), t (triplet), and m (multiplet). Electron Spray Ionization (ESI) and high resolution mass spectra (HRMS) were recorded on QSTARXL hybrid

MS/MS system (Applied Bio Systems, USA) under electro spray ionization. Photophysical properties were carried out by using Jasco V-550 spectrophotometer and Horiba Jobin Yvon Fluorolog-3 spectroflurimeter.

Method for the synthesis of 7-amino-4-methylcoumarin (4)

Methyl 4-methyl-2-oxo-2*H*-chromen-7-ylcarbamate (**3**) (3.3g, 14.16m.mol) was suspended in a mixture of 1:1 concentrated H_2SO_4 and CH_3COOH and refluxed at 125 ^{0}C for 2h. The reaction mixture was cooled to room temperature and the brown solution was drizzled in to excess crushed ice and brought to pH 9 with 1N NaOH solution. Then the resulting light yellow color solid was filtered and washed with water, dried in vacuum and recrystallized in ethanol to get the target compound **4** in 70 % yield.

Preparation of 4-methyl-7-(prop-2-ynylamino)-2H-chromen-2-one (5)

To the stirred solution of compound **4** (2.5 g, 14.29 mmol) in anhydrous acetonitrile (25 mL) was added anhydrous K_2CO_3 (5.8 g. 42.87 mmol) in lot wise at room temperature under N_2 atmosphere. A solution of propargyl bromide (2.5g / 1.92 mL, 21.43 mmol, 80% w/v in toluene) was added to the reaction mixture at 0 ^{0}C over a period of 20 min. and the reaction mixture was allowed to room temperature then heated to 60 ^{0}C for 8-9 hrs. After completion of the reaction, it is cooled to RT, filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in EtOAc (50 mL), and washed with water and dried over anhydrous Na_2SO_4. The compound was purified by column chromatography (silica gel 60-120) using the mobile phase $CHCl_3$: EtOAc (9:1) as an eluent to afford the pure compound **5**.

Typical experimental procedure for the preparation of compound (7a-q)

Compound **5** (1.0 mmol) was dissolved in dry THF (10 ml) and catalytic amount of copper iodide was added. To this, corresponding azides **6a-q** (1.0 mmol) in dry THF was added slowly while stirring at room temperature under nitrogen atmosphere for 3-6h. Later, the solvent was removed under reduced pressure and the residue was diluted with distilled water and extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to get the final products **7a-q**. The crude products were purified by column chromatography with ethyl acetate in hexane.

BIOLOGICAL ASSAY

The cell lines, HeLa, PANC 1, HepG2, SKNSH, MDA MB 231 and IMR 32 (cervical, pancreatic, hepatic, neuroblastoma, breast and neuroblastoma) which were used in this study were procured from American Type Culture Collection (ATCC), United States. The synthesized tested compounds were evaluated for their *invitro* antiproliferative activity in these six different human cancer cell lines. A protocol of 48h continuous drug exposure was used and a SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 ^{0}C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 μL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 ^{0}C, 5 % CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 hrs with different doses (0.01, 0.1, 1, 10,100 μM) of prepared derivatives**.** After 48 hours incubation at 37 ^{0}C, cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 ^{0}C for 1h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein–bound dye was dissolved in 10mM tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, and USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

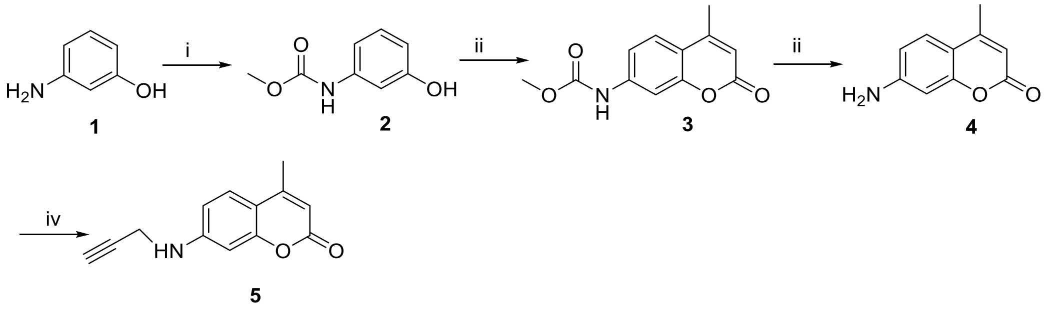
[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz [(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

Values were calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested. Three dose response parameters were calculated for each experimental agent. Growth inhibition of 50 % (GI_{50}) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

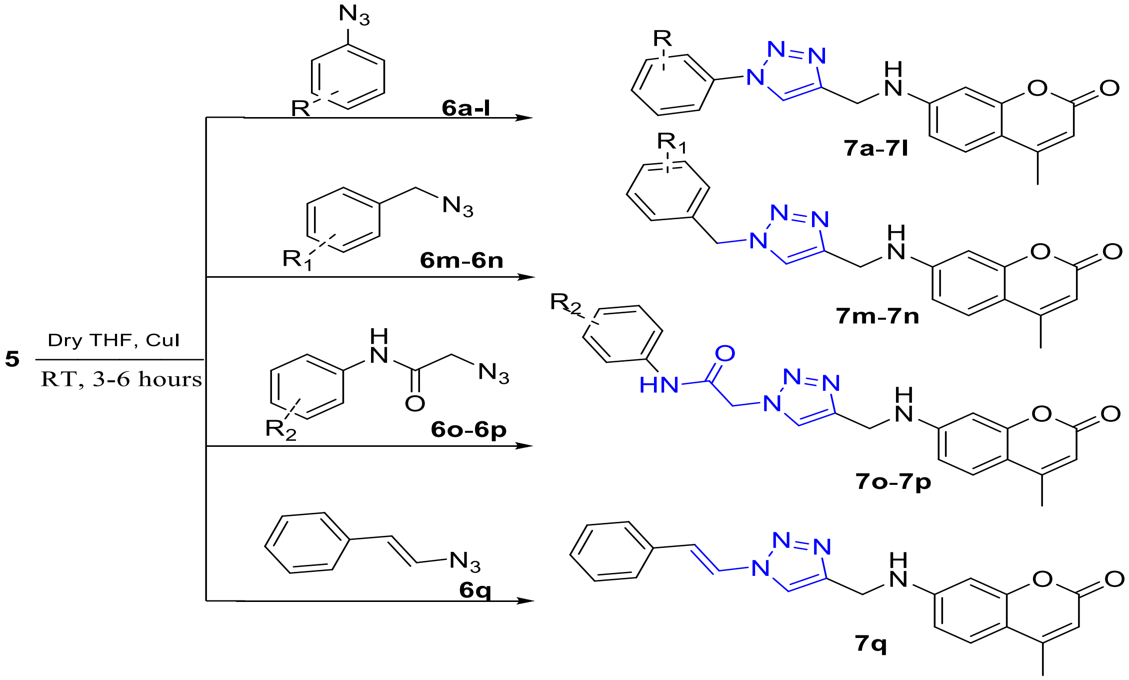
RESULTS AND DISCUSSION

Chemistry

The synthesis of 7-amino-4-methyl coumarin (**4**) was synthesized by the condensation of 3-amino-phenol with methylchloroformate and ethyl acetoacetate [25]. The coupling of compound **4** with propargyl bromide [26] led to the formation of precursor alkyne **5** which was treated with a series of required azides **6a-q** [27] to get 1,2,3-triazoles. The strategic 1,2,3-triazoles **7a-q** synthesis was carried over alkyne **5** in the presence of catalytic Cu (I) in dry THF with azides **6a-q**. All the coumarin based 1,2,3-triazole hybrid compounds **7a-q** were well characterized by IR, ^{1}H,^{13}C NMR and HRMS data. Compounds **7a-q** showed IR absorption bands ranging from 3335-3271 cm^{-1} for N-H, 3092-3026 cm^{-1} for aromatic C-H and 1505-1480 cm^{-1} for C=N stretching. The conversion ratio of alkyne to triazoles was monitored by ^{1}H & ^{13}C NMR which showed methylene and triazole CH groups as signals at δ 4.46-5.20 (triazole-C***H₂***) & 7.96-8.91 (N-C***H***=C-) and the corresponding ^{13}C signals at 37.8-45.1 & 129.2-134.4 ppm respectively. Moreover, triazole formation from **5** was further confirmed by the disappearance of the alkyne proton signal at δ 2.30 ppm. Thus, the click reaction was efficient, as evidenced by near-quantitative fictionalization.



Reagents and conditions: (i) Methyl chloroformate, NaHCO$_3$, EtOAc, rt, 30 min. (ii) Ethylacetoacetate, conc. H$_2$SO$_4$, r.t., 2h (iii) H$_2$SO$_4$, AcOH(1:1), 125 °C, 3h (iv) Propargyl bromide, K$_2$CO$_3$, ACN, 60^{0}C, 6h



Scheme 1

CYTOTOXIC EVALUATION

Cytotoxic assay was carried out to evaluate the effect of the synthesized compounds on cervical cancer (Hela), pancreatic cancer (PANC1), hepatic cancer (HepG2), human neuroblastma (SKNSH), breast (MDA MB) and neuroblastma (IMR 32) cell lines *in vitro* method[28]. The clinically applied anticancer agent, doxorubicin, was used as positive control for cytotoxicity assays at concentrations of 100 µg/mL and 10 µg/mL in each 96-well plate. The clinically applied anticancer agent, doxorubicin, was used as positive control for cytotoxicity assays at concentrations of 100 µg/mL and 10 µg/mL in each 96-well plate. The GI$_{50}$ values were shown in Table-1 and the values are the average of the triplicate analysis. The results of cytotoxic activity indicated that the some of the title compounds (**7h**, **7i** and **7l**) showed more potent activity against IMR32 and SKNSH cell lines while the compounds **7c**, **7f** and **7g** exhibited moderate activity against to the investigated cell lines compared to the standard drug. Compound **7h** exhibited potent activity (0.015±0.001 µM on IMR 32) almost equivalent to that of the standard drug. It was therefore concluded that the presence of electron withdrawing group like 3-nitro substituted 1,2,3-triazole on coumarin moiety. Meanwhile it was observed that these 2-acetyl and 2,4,5-trimethoxy substituted compounds (**7i** and **7l**) exhibited in contrast to SKNSH and IMR32 cell lines with 0.02±0.01 and 0.02±0.001 µM. Also, the compounds having electron donating groups like 4-methoxy in **7c,** 4-iodo in **7f** and 3,4-dimethoxy in **7g** are selectively reticent PANC 1, Hep G2 and IMR 32 cell lines with 0.07±0.01, 0.06±0.01 and 0.08±0.01 µM, respectively. Remaining all the derivatives are weakly potent against the Hela, MDA MB cell lines.

Table 1. Percentage growth inhibition (GI%) of compounds (7a-q) at concentration GI$_{50}$,10µM

S.No.	Hela GI $_{50}$	PANC 1 GI $_{50}$	HepG2 GI $_{50}$	SKNSH GI $_{50}$	MDA MB 231 GI $_{50}$	IMR 32 GI $_{50}$
7a	1.8±0.6	0.4±0.06	50.7±0.7	>100	3.1±0.8	1.17±0.5
7b	31.4±3.0	2.2±0.2	20.4±2.7	0.17±0.05	2.6±0.48	>100
7c	0.9±0.1	0.07±0.01	>100	>100	53.4±0.65	14.0±0.2
7d	15.4±0.2	>100	2.9±0.4	1.7±0.9	11.6±0.6	0.71±0.37
7e	>100	>100	3.8±0.5	0.47±0.1	2.8±0.4	>100
7f	21.75.4	>100	0.06±0.01	4.03±0.3	2.3±0.26	>100
7g	1.8±0.2	0.1±0.05	0.1±0.02	>100	4.3±0.4	0.08±0.01
7h	8.7±0.2	0.03±0.01	0.9±0.5	>100	>100	0.015±0.001
7i	3.2±0.4	0.04±0.01	0.1±0.09	0.02±0.01	2.5±0.8	>100
7j	7.7±0.17	16.9±0.5	2.4±0.2	>100	3.6±0.37	0.57±0.25
7k	1.4±0.8	54.1±7.6	1.20±0.1	>100	71.9±0.43	0.13±0.01
7l	4.9±0.6	0.16±0.02	>100	0.24±0.1	>100	0.02±0.001
7m	3.1±0.1	5.0±0.6	1.6±0.8	>100	26.1±0.16	0.51±0.06

7n	9.2±4.3	>100	18.5±0.7	17.3±0.6	43.9±0.9	0.42±0.07
7o	3.1±2.4	>100	6.1±.8	0.86±0.3	10.7±1.5	0.31±0.05
7p	11.1±0.9	0.1±0.03	0.7±0.03	46.7±2.3	1.85±0.2	0.22±0.08
7q	3.2±2.3	0.14±0.1	>100	>100	1.9±0.7	0.3±0.07
Combretastatin	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Doxorubicin	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

PHOTOPHYSICAL PROPERTIES

Coumarins are widely used in the field of medicine, biology, cosmetics and fluorescent dyes [29]. They have been identified as efficient fluorophores [30] with good emission quantum yields and are also used as materials for lasers in organic light emitting devices (OLED) [31], optical brighteners [32], non-linear optical chromophores and fluorescent labels[33]. As there is lot of importance for these properties, we have further concentrated our study on the photophysical properties of the synthesized coumarin based triazole hybrids **7a-q** for the development of lead compounds. The UV (absorption) and fluorescence (emission) properties of **7a-q** are summarized in the Table 2.

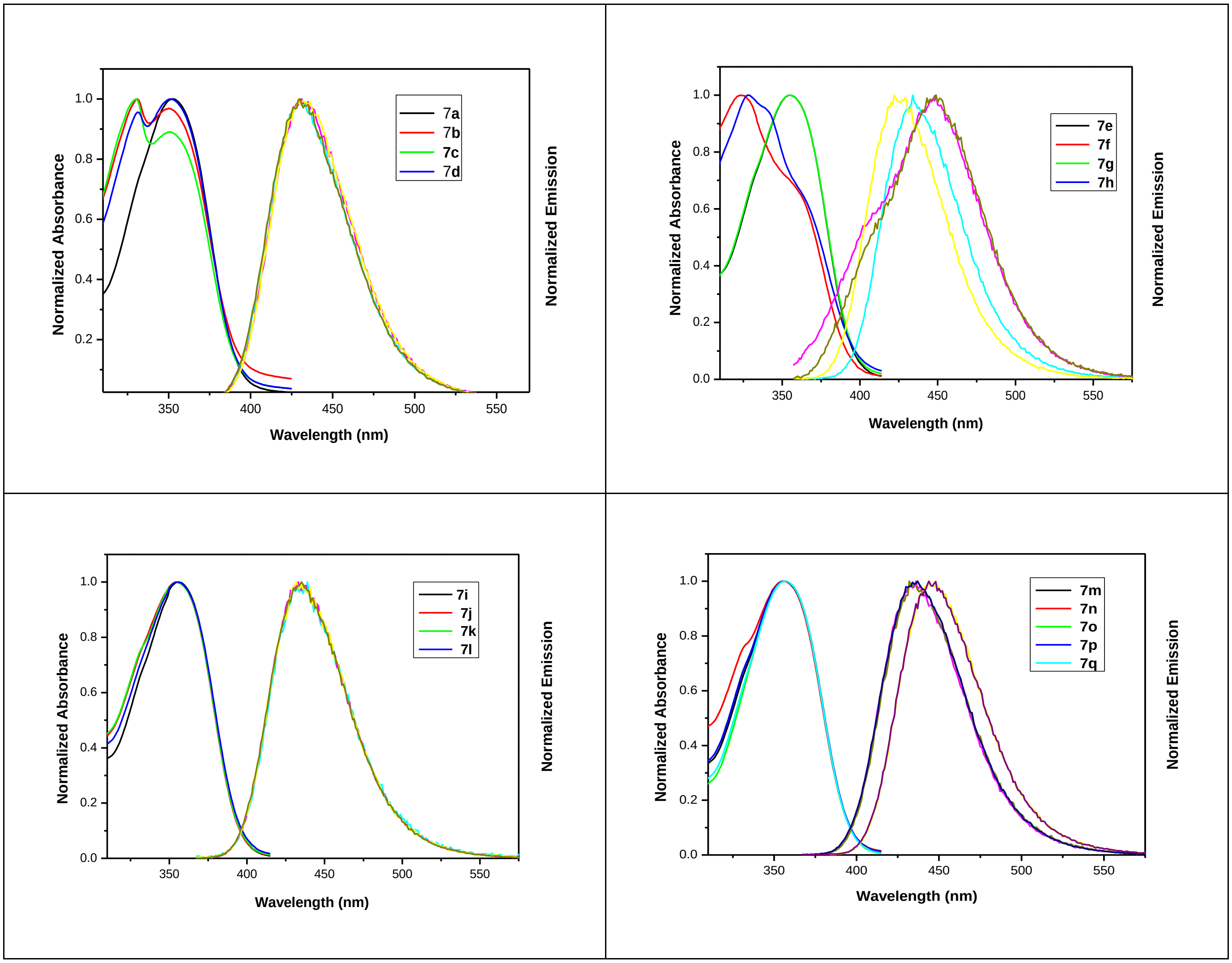


Figure 1 UV and fluorescence spectra of synthesized compounds 7a-q

The UV (absorption) and fluorescence (emission) properties of synthesized compounds were carried out at Crop Protection Chemical Division, CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad. All solvents were of spectroscopic grade and were used as received. The UV (absorption) spectra were recorded using Jasco V-550 spectrophotometer. Fluorescence measurements were carried out with a Horiba Jobin Yvon Fluorolog-3 Specrtofluorimeter. The absorption and fluorescence spectra of coumarin based 1,2,3-triazole derivatives carried out in DMSO solvent at 1 × 10^{-5} M concentration.

Table 2 UV ($\lambda_{max.abs}$) and Fluorescence ($\lambda_{max.em}$) values for compounds (7a–q)

Compounds	λ_{abs} (nm)^a (ε)^b	λ_{em}(nm)^a
7a	357 (16300)	432
7b	356 (21200)	434
7c	355 (31200)	436
7d	355 (21800)	432
7e	355 (18900)	434
7f	354 (11300)	435
7g	356 (21400)	433
7h	329 (18700)	428
7i	328 (23500)	431
7j	355 (23200)	433
7k	355 (18900)	434
7l	355 (14200)	434
7m	356 (15600)	435
7n	356 (20100)	436
7o	357 (25200)	432
7p	357 (16700)	437
7q	357 (25800)	434

^{a} Recorded in MeOH (1 x 10^{-5} M concentration), ^{b} molar extinction coefficient ($mol^{-1}cm^{-1}$)

SPECTRAL DATA

4-methyl-7-(prop-2-ynylamino)-2H-chromen-2-one (**5**)

Yield: 70 %; yellow solid; m.p: 148-150 ^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 (d, 1H, *J*= 8.6 Hz), 6.64 (m, 2H), 6.04 (s, 1H), 4.52 (br), 4.02 (d, 2H, *J* = 5.5 Hz), 2.40 (s, 3H), 2.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6,155.3, 153.6, 152.9, 126.1, 111.1, 108.8, 107.3, 98.4, 73.4, 78.3, 38.9, 17.9; ESI-MS *m/z*: 213.08 (100.0%), 214.08 $[M+H]^+$, HRMS (ESI *m/z*) calcd for $C_{13}H_{12}NO_2$: 214.0862, $[M+H]^+$; found: 214.0858.

4-Methyl-7-((1-p-tolyl-1H-1,2,3-triazol-5-yl)-methylamino)-2H-chromen-2-one (**7a**).

Yield: 75%; pale yellow color solid, m.p: 198-200 ^{0}C; IR (KBr): 3334 (N-H), 3260 (=C-H), 2923 (C-H), 1694 (lactones), 1605 (C=C of triazole) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.69 (s, 1H), 7.75 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 1H, *J* = 8.6 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.18 (t, 1H, *J* = 5.4 Hz), 6.71 (dd, 1H, *J* = 6.4, 2.2 Hz), 5.93 (s, 1H), 4.47 (d, 2H, *J* = 5.4 Hz), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.6, 155.4, 153.7, 151.8, 145.6, 138.2, 134.3, 130.2, 125.9, 121.1, 119.8, 110.4, 109.1, 107.8, 96.8, 37.9, 20.5, 17.9; MS (ESI *m/z*): 347.14 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{20}H_{19}N_4O_2$: 347.1434 $[M+H]^+$; found: 347.1453.

4-Methyl-7-((1-phenyl-1H-1,2,3-triazol-5-yl)methylamino)-2H-chromen-2-one (**7b**).

Yield: 75%; pale yellow color solid, m.p: 189-191 ^{0}C; IR (KBr): 3334 (N-H), 3260 (=C-H), 2923 (C-H), 1694 (lactones), 1684 (C=C of triazole), 1155 (C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.09 (s, 1H), 7.61 (d, 2H, *J* = 7.5 Hz), 7.56 (t, 2H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 8.6 Hz), 7.41 (t, 1H, *J* = 7.5 Hz), 6.69 (dd, 1H, *J* = 6.4, 2.2 Hz), 5.93 (s, 1H), 4.47 (d, 2H, *J* = 5.4 Hz), 2.36 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.6, 155.43, 153.7, 151.8, 145.6, 138.2, 134.3, 130.2, 125.9, 121.1, 119.8, 110.4, 109.2, 107.8, 96.8, 37.9, 17.98; MS (ESI *m/z*): 333.1 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{19}H_{17}N_4O_2$: 333.1354 $[M+H]^+$; found: 333.1365.

7-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-5-yl)methylamino)-4-Methyl-2H-chromen-2-one (7c).

Yield: 77 %; light yellow solid, m.p: 168-170 ^{0}C; IR (KBr): 3332 (N-H), 3012 (=C-H), 2923 (C-H), 1703 (lactones), 1609 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.07 (s, 1H),7.72- 7.64 (m, 3H), 7.49 (dd, 1H, *J* = 6.4, 2.2 Hz), 7.44 (d, 1H, *J* = 2.2 Hz), 7.09 (d, 2H, *J* = 9.1 Hz), 6.33(d, 1H, *J* = 2.1 Hz), 4.41 (d, 2H, *J*= 5.4 Hz), 3.94 (s, 3H), 2.50 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d_6) δ (ppm): 160.6, 159.3, 155.4, 153.7, 151.8, 145.6, 138.2, 134.4, 130.2, 125.9, 121.9, 119.8, 110.4, 109.2, 107.8, 96.8, 55.6, 37.9, 17.9; MS (ESI *m/z*): 363.1 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{20}H_{18}N_4O_3$: 363. 14517 $[M+H]^+$; found: 363. 14697.

7-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-yl)methylamino)-4-Methyl-2H-chromen-2-one (7d)

Yield 71%; light yellow solid, m.p: 181-183 ^{0}C; IR (KBr): 3306 (N-H), 3092 (=C-H), 2924 (C-H), 1703 (lactone), 1609 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.05 (s, 1H), 7.54 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 6.71 (dd, 1H, *J* = 6.4, 2.2 Hz), 6.56 (d, 1H, *J* = 2.1 Hz), 5.98 (s, 1H), 4.62 (d, 2H, *J* = 6.0 Hz), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.6, 155.4, 153.7, 151.8, 145.5, 135.3, 132.8, 129.8, 125.9, 121.6, 121.4, 110.5, 109.2, 107.8, 96.8, 37.8, 17.9; MS (ESI *m/z*): 367.09, $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{19}H_{16}O_2N_4Cl$: 367.0956 $[M+H]^+$; found: 367.0979.

7-((1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-Methyl-2H-chromen-2-one (7e). Yield 71%; light yellow solid, m.p: 155-157 ^{0}C; IR (KBr): 3306 (N-H), 3092 (=C-H), 2924 (C-H), 1707 (lactone), 1610 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.01 (s, 1H), 7.86 (d, 2H, *J* = 6.0 Hz), 7.69 (d, 2H, *J* = 6.0 Hz), 7.43 (d, 1H, *J* = 6.5 Hz), 6.71 (dd, 1H, *J*

= 6.5, 2.3 Hz), 6.56 (d, 1H, *J* = 2.2 Hz), 5.96 (s, 1H), 4.56 (d, 2H, *J* = 5.8 Hz), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm)**:** 160.6**,** 155.4, 153.6, 151.8, 145.9, 135.7, 132.7, 125.9, 125.9, 121.8, 121.1, 110.4, 107.8, 107.8, 96.8, 37.8, 17.9; MS (ESI *m/z*): 413.2 [M+H]$^+$; HRMS (ESI *m/z*) calcd for $C_{19}H_{16}BrN_4O_2$: 413.2688 [M+H]$^+$; found: 413.2730.

7-((1-(4-Iodophenyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7f).

Yield 71%; light yellow solid, m.p**:** 140-142 ^{0}C; IR (KBr): 3345 (N-H), 3271 (=C-H), 2923 (C-H), 1699 (lactone), 1610 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.06 (s, 1H), 7.86 (d, 2H, *J* = 6.0 Hz), 7.69 (d, 2H, *J* = 6.0 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 6.71 (dd, 1H, *J* = 6.5, 2.8 Hz), 6.56 (d, 1H, *J* = 2.5 Hz), 5.96 (s, 1H), 4.56 (d, 2H, *J* = 5.8 Hz), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.5**,** 155.4, 153.7, 151.8, 145.9, 135.3, 132.8, 129.8, 125.9, 121.6, 121.3, 110.4, 109.1, 107.8, 95.8, 38.8, 17.9**;** MS (ESI *m/z*): 481.2 [M+Na]$^+$; HRMS (ESI *m/z*) calcd for $C_{19}H_{15}IO_2N_4Na$: 481.2565 [M+Na]$^+$, found: 481.2673.

7-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7g).

Yield 71%; light yellow solid, m.p**:** 168-170 ^{0}C; IR (KBr): 3332 (N-H), 3012 (=C-H), 2923 (C-H), 1703 (lactones), 1609 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.67 (s, 1H), 7.72-7.64 (m, 3H), 7.49 (dd, 1H, *J* = 6.5, 2.2 Hz), 7.44 (d, 1H, *J* = 7.1 Hz), 7.09 (d, 1H, *J* = 7.1 Hz), 6.33 (d, 1H, *J* = 2.0 Hz), 5.11 (s, 2H), 3.94 (s, 6H), 2.50 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.6, 159.2, 155.4, 153.7, 151.8, 145.5, 138.2, 134.4, 130.1, 125.9, 121.9, 118.8, 119.1, 110.4, 109.1, 107.8, 96.8, 55.6, 37.9, 17.9; MS (ESI *m/z*): 393.2 [M+H]$^+$; HRMS (ESI *m/z*) calcd for $C_{21}H_{21}N_4O_4$: 393.2474 [M+H]$^+$; found: 393.2531.

4-Methyl-7-((1-(3-nitrophenyl)-1H-1,2,3-triazol-5-yl)methylamino)-2H-chromen-2-one (7h).

Yield 70 %; light yellow solid, m.p**:** 157-159 ^{0}C; IR (KBr): 3447 (N-H), 3092 (=C-H), 2924 (C-H), 1711 (lactone), 1614 (C=C of triazole), 1550 (-NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm)**:** 8.91 (s, 1H), 8.15 (d, 2H, *J* = 8.8 Hz), 8.07 (d, 2H, *J* = 8.8 Hz), 7.46 (d, 1H, *J* = 8.6 Hz), 7.22 (t, 1H, *J* = 5.6 Hz), 6.71 (dd, 1H, *J* = 6.5, 2.1 Hz), 6.57 (d, 1H, *J* = 2.2 Hz), 5.94 (s, 1H), 4.50 (d, 2H, *J* = 5.6 Hz), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 159.6, 154.6, 152.9, 148.4, 145.5, 145.0, 137.0, 131.4, 131.3, 125.9, 125.5, 123.0, 117.6, 114.6, 114.5, 113.7, 109.3, 107.8, 45.1, 17.9; MS (ESI *m/z*): 378.12 [M+H]$^+$; HRMS (ESI *m/z*) calcd for $C_{19}H_{16}O_4$ N_5: 378.1215 [M+H]$^+$; found: 378.1208.

7-((1-(2-Acetylphenyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7i).

Yield 74%; light yellow solid, m.p: 180-182 ^{0}C; IR (KBr): 3306 (N-H), 3093 (=C-H), 2925 (C-H), 1708 (lactone), 1702 (acetyl), 1610 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm)**:** 8.06 (s, 1H), 7.85 (t, 1H, *J*= 5.6 Hz), 7.54-7.36 (m, 2H), 7.21 (d, 1H, *J* = 8.3 Hz), 6.52 (dd, 1H, *J* = 8.3, 2.2 Hz), 6.46 (d, 1H, *J* = 2.2 Hz), 5.83 (s, 1H), 4.46 (d, 2H, *J* = 6.0 Hz), 2.68 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 196.5, 161.7**,** 155.7, 152.8, 150.5, 145.8, 138.5, 137.7, 130.2, 128.5, 125.7, 124.7, 119.8, 119.6, 111.3, 110.7, 110.0, 98.6, 39.2, 29.6, 18.5; MS (ESI *m/z*): 375.19 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{21}H_{19}N_4O_3$: 375.3409 $[M+H]^+$; found: 375.3501.

7-((1-(4-Acetylphenyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7j)

Yield 73%; light yellow solid, m.p: 169-171 ^{0}C; IR (KBr): 3306 (N-H), 3092 (=C-H), 2924 (C-H), 1707 (lactone), 1704 (acetyl), 1610 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.09 (s, 1H), 7.94 (d, 2H, *J* = 8.8 Hz), 7.74 (d, 2H, *J* = 8.6 Hz), 6.71 (dd, 1H, *J* = 6.8, 2.2 Hz), 6.57 (d, 1H, *J* = 2.2 Hz), 5.94 (s, 1H), 5.20 (d, 2H, *J* = 5.6 Hz), 2.62 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 196.6, 160.5, 155.3, 153.7, 151.6, 145.6, 138.3, 134.3, 130.2, 125.9, 121.3, 119.7, 110.4, 109.2, 107.8, 96.8, 37.9, 28.9, 18.6; MS (ESI *m/z*): 375.19 $[M+H]^+$, HRMS (ESI *m/z*) calcd for $C_{21}H_{19}O_3N_4$: 375.3409, found: 375.3511.

7-((1-(6-Chloropyridin-2-yl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7k).

Yield 70%; light yellow solid, m.p:220-222 ^{0}C; IR (KBr): 3306 (N-H), 3092 (=C-H), 2924 (C-H), 1702 (lactone), 1610 (C=C of triazole), (1609 (C=N, in pyridine) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.26 (s, 1H), 8.08 (s, 1H), 8.04-7.99 (m, 2H), 7.39 (d, 1H, *J* = 8.3 Hz), 6.63 (dd, 1H, *J* = 6.3, 2.2 Hz), 6.55 (d, 1H, *J* = 2.2 Hz), 6.0 (s, 1H), 4.62 (d, 2H, *J* = 5.6 Hz), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.5, 155.4, 153.6, 151.7, 149.3, 146.2, 141.2, 132.7, 131.2, 125.9, 125.1, 121.6, 110.4, 109.1, 107.8, 96.8,37.8, 17.9; MS (ESI *m/z*): 368.2 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{18}H_{15}ClO_2N_5$: 368.2158 $[M+H]^+$; found: 368.2165.

4-Methyl-7-((1-(2, 4, 5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylamino)-2H-chromen-2-one (7l).

Yield 65%, light yellow solid, m.p: 170-172 ^{0}C, IR (KBr): 3343 (N-H), 3140 (=C-H), 2923 (C-H), 1697 (lactones), 1611 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.08 (s, 1H), 7.45 (d, 1H, *J* = 8.0 Hz), 6.71 (s, 1H), 6.53 (dd, 1H, *J* = 6.5, 2.2 Hz), 6.47 (s, 1H), 6.36 (d, 1H, *J* = 2.1 Hz), 5.96 (s, 1H), 4.46 (d, 2H, *J* = 5.8 Hz), 3.74 (s, 9H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm)**:** 160.6, 155.4, 153.6, 153.4, 151.8, 145.5, 137.2, 132.4, 125.8, 121.5, 110.4, 109.1, 107.8, 97.8, 96.8, 60.1, 56.2, 38.0, 17.9; MS (ESI *m/z*): 423.16 $[M+H]^+$; HRMS (ESI *m/z*) calcd for $C_{22}H_{23}N_4O_5$: 423.1663 $[M+H]^+$; found: 423.1688.

7-((1-Benzyl-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7m).

Yield 75%; light yellow solid, m.p: 149-151 ^{0}C; IR (KBr): 3331 (N-H), 3257 (=C-H), 2922 (C-H), 1697 (lactones), 1607 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm)**:** 7.96 (s, 1H), 7.43 - 7.32 (m, 5H), 6.97 (dd, 1H, *J* = 6.5, 2.2 Hz), 6.64 (d, 1H, *J* = 2.2 Hz), 6.56 (d, 1H, *J* = 6.5 Hz), 6.01 (s, 1H), 5.05 (s, 2H), 4.59 (d, 2H, *J* = 3.7 Hz), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.6, 160.2, 155.4, 153.7, 151.8, 145.5, 138.2, 134.4, 130.1, 125.9, 121.9, 119.8, 113.4, 113.1, 107.8, 96.8, 57.6, 55.6, 37.9, 17.9; MS (ESI): *m/z* 347.4 [M+H]$^+$, HRMS (ESI *m/z*) calcd for $C_{20}H_{19}N_4O_2$: 347.4315 [M+H]$^+$; found: 347.4395.

7-((1-(3-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methylamino)-4-methyl-2H-chromen-2-one (7n).

Yield 73%; light yellow solid, m.p: 150-152 ^{0}C; IR (KBr)**:** 3331 (N-H), 3257 (=C-H), 2922 (C-H), 1697 (lactones), 1607 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm)**:** 7.76 (s, 1H), 7.43 (d, 1H, *J* = 6.3 Hz), 7.20 (t, 1H, *J* = 7.2 Hz), 7.02 (s, 1H), 6.87 (dd, 1H, *J* = 6.3, 2.2 Hz), 6.64 (d, 1H, *J* = 7.2 Hz), 6.56 (d, 1H, *J* = 7.1 Hz), 6.34 (d, 1H, *J* = 2.2 Hz), 6.01 (s, 1H), 5.03 (s, 2H), 4.62 (d, 2H, *J* = 3.7 Hz), 3.83 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6,75 MHz) δ (ppm): 160.6, 159.6, 157.2, 155.4, 153.7, 151.8, 145.5, 138.2, 134.4, 130.1, 125.9, 121.6, 119.6, 113.4, 113.1, 107.8, 96.8, 57.6, 55.6, 37.9, 17.9 ppm; MS (ESI *m/z*): 376.15 [M+H]$^+$; HR-MS (ESI *m/z*) calcd for $C_{21}H_{21}N_4O_3$: 376.1573 [M+H]$^+$; found: 376.1595.

2-(4-((4-Methyl-2-oxo-2H-chromen-7-ylamino)methyl)-1H-1,2,3-triazol-1-yl)-N-phenyl acetamide (7o).

Yield 71%; light yellow solid, m.p: 215-217 ^{0}C; IR (KBr): 3334 (N-H), 3260 (=C-H), 2923 (C-H), 1694 (lactones), 1605 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 10.45 (s, amide N-H), 8.04 (s, 1H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.45 (d, 1H, *J* = 8.6 Hz), 7.32 (t, 2H, *J* = 6.5 Hz), 7.08 (d, 1H, *J* = 7.3 Hz), 6.70 (dd, 1H, *J* = 8.8, 2.2 Hz), 6.54 (d, 1H, *J* = 2.0 Hz), 5.93 (s, 1H), 5.30 (s, 2H), 4.99 (s, 1H), 4.43 (d, 2H, *J* = 5.8 Hz), 2.30 (s, 3H); ^{13}C NMR(DMSO-d_6, 75 MHz) δ (ppm): 163.8, 160.6, 155.4, 153.7, 151.8, 145.5, 138.1, 134.3, 130.1, 128.2, 125.9, 121.1, 119.8, 110.4, 109.1, 107.8, 59.8, 37.9, 17.9; MS (ESI *m/z*): 412.13 [M+Na]$^+$; HRMS (ESI *m/z*) calcd for $C_{21}H_{19}N_5O_3Na$: 412.1380 [M+Na]$^+$; found: 412.1397.

2-(4-((4-Methyl-2-oxo-2H-chromen-7-ylamino)methyl)-1H-1,2,3-triazol-1-yl)-N-p-tolylacetamide (7p).

Yield 71%; light yellow solid, m.p: 219-221 ^{0}C; IR (KBr): 3334 (N-H), 3260 (=C-H), 2923 (C-H), 1694 (lactones), 1605 (C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 10.45 (s, amide N-H), 8.04 (s, 1H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.45 (d, 1H, *J* = 6.7 Hz), 7.24 (d, 2H, *J* = 7.7 Hz), 6.70 (dd, 1H, *J* = 6.7, 2.2 Hz), 6.54 (d, 1H, *J* = 2.2 Hz), 5.93 (s, 1H), 5.30 (s, 2H), 4.44 (d, 2H, *J* = 5.8 Hz), 2.24 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.2, 160.7, 155.5, 153.8, 151.9, 144.4, 138.3, 129.2, 125.9, 125.4, 124.5, 123.7, 119.1, 110.5, 109.1, 107.7, 52.1, 37.8, 20.4 , 17.9; MS (ESI *m/z*): 426.15 [M+Na]$^+$; HRMS (ESI *m/z*) calcd for $C_{22}H_{21}O_3N_5Na$: 426.1536 [M+Na]$^+$; found: 412.1558.

4-Methyl-7-((1-styryl-1H-1,2,3-triazol-4-yl)methylamino)-2H-chromen-2-one (7q).

Yield 75%; light yellow solid, m.p**:**165-166 ^{0}C; IR (KBr): 3336 (N-H), 3115 (=C-H), 2922 (C-H), 1691 (lactones), 1631 (C=C of trans), 1613(C=C of triazole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.05 (s, 1H), 7.45-7.25 (m, 6H), 7.12 (d, 1H , *J* = 6.8 Hz), 6.65-6.69 (dd, 1H, *J* = 6.8, 2.2 Hz,), 6.52 (s, 1H), 6.49 (d, 1H, *J* = 6.0 Hz,), 5.92 (s, 1H), 5.12 (s, 1H, -NH), 4.39 (d, 2H, *J* = 5.7 Hz,), 2.29 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm)**:** 160.6, 155.4, 153.6, 151.8, 144.8, 135.6, 133.3, 135.6, 133.3, 128.6, 128.0, 126.4, 125.8, 123.7, 122.8, 110.4, 109.1, 107.7, 96.8, 37.9, 17.9; MS (ESI *m/z*): 359 [M+H]$^+$; HRMS (ESI *m/z*) calcd for $C_{21}H_{19}N_4O_2$: 359.1340 [M+H]$^+$; found: 359.1510.

CONCLUSION

7-Amino-4-methyl-coumarin nucleus bearing 1,2,3-triazole derivatives in a single molecular frame work were efficiently synthesized and in vitro cytotoxic activity and photophysical studies were carried out. The cytotoxic activity revealed that these compounds are selective in their action as three of the synthesized compounds**7h**, **7i** and **7l** are exhibited potent activity against IMR32 and SKNSH cell lines. Particularly **7h** proved to be the best analogue with GI_{50} of 0.015 µM against IMR 32 cell line which is equal to that of the standard drug.

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